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The cost-effectiveness of inhaled fluticasone propionate and budesonide in the treatment of asthma in adults and children

N. C. BARNES*, R. M. A. THWAITES†, AND M. J. PRICE†

*Department of Respiratory Medicine, London Chest Hospital, Bonner Road, London E2 9JX, U.K.
†Glaxo Wellcome Research and Development, Greenford Road, Greenford, Middlesex UB6 0HE, U.K.

Inhaled corticosteroids form the mainstay of the treatment and management of asthma and the results of a meta-analysis comparing two of the most frequently prescribed inhaled corticosteroids, fluticasone propionate and budesonide, administered in a clinically equivalent 1:2 dose ratio to 1980 patients with asthma, demonstrated that fluticasone propionate had an improved efficacy:safety ratio. However, limited data are available on the relative economic benefits of fluticasone propionate and budesonide. The database for clinically relevant parameters, for which the efficacy:safety meta-analysis had demonstrated statistical significance between the two corticosteroids, was used for this pharmacoeconomic analysis. Treatment with fluticasone propionate was more cost-effective than budesonide with respect to improvement in morning peak expiratory flow rate, successfully treated weeks, symptom-free days, symptom-free 24 h and episode-free days. The costs of treatment for fluticasone propionate and budesonide were £7.78 per week and £12.33 per week, respectively. The main contributing factor to the higher costs of budesonide was the higher cost of health care contacts, which were £4.53 per week for budesonide and £0.57 per week for fluticasone propionate. The pharmacoeconomic difference increased in favour of fluticasone propionate as the criteria for success were made more stringent. These results demonstrate that, for asthma patients requiring modification of therapy treatment with fluticasone propionate is more effective and also cheaper, in terms of overall health-care costs, than treatment with budesonide.

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Introduction

Asthma is an increasingly common, chronic disease in both adults and children (1,2) which imposes a substantial burden on the patient, on the health-care system and society as a whole in terms of mortality, morbidity and economic costs (3). In the absence of a cure for the disease, the goals of asthma care are to avoid mortality, reduce exacerbations, control symptoms, optimize lung function and allow patients to lead lives that are as normal as possible, with cost-effective management approaches. Inhaled corticosteroids, which reduce mortality, exacerbations and the frequency and severity of symptoms, and improve patients' health-related quality of life, form the mainstay of treatment for all but those with mild intermittent disease. Consequently, national and international guidelines for the management of asthma recommend the use of inhaled corticosteroids as first-line therapy in mild persistent, moderate and severe asthma (4,5).

Of the inhaled corticosteroids currently available, fluticasone propionate and budesonide are both commonly prescribed. Fluticasone propionate possesses the lowest degree of oral bioavailability and longest pulmonary residence time, and, once absorbed into the circulation, is rapidly metabolized (6). Fluticasone propionate is now recommended for use in asthma at half the dose of other inhaled steroids (4,7,8). This was confirmed in a recent meta-analysis involving studies in adults and children treated with either fluticasone propionate or budesonide administered at clinically equivalent doses, which demonstrated that fluticasone propionate is more effective than budesonide and at least as safe when given at approximately half the microgram dose (9).

Although there is clinical evidence to support the superior efficacy and safety of fluticasone propionate at half the microgram dose, there are limited data available on the relative economic benefits of fluticasone propionate and budesonide. However, evidence of superior efficacy and safety should be accompanied by economic assessments to help health care payers determine whether additional improvements in health are worth paying for. Consequently, this article presents the results of an economic analysis of the fluticasone propionate/budesonide database that was used for the clinical meta-analysis and is the first such analysis based on a large population.

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Correspondence should be addressed to: R. M. A. Thwaites, Global Health Outcomes, Glaxo Wellcome Research and Development, 317 Greenford Road, Greenford UB6 0HE, U.K.

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In evaluating the economic benefits of asthma management, measures of effectiveness need to be chosen which reflect the benefits being paid for. In a comparison between two treatments, these might reflect the willingness to pay for improvements in lung function, for better control of symptoms and for fewer exacerbations. There is no single, widely accepted endpoint which captures in an economic sense the benefits of asthma treatment, though each of the above has been addressed in separate studies.

Three different approaches have been adopted to address the multiple objectives of asthma management. Most studies have focused on a single outcome measure, such as symptom-free days (10), improvement in lung function (11) or improvement in health-related quality of life (12). Second, more than one outcome measure can be reported. In a study demonstrating the value of inhaled corticosteroids, two measures were reported to capture separately the improvements in lung function and symptom control (13). Finally, in a study demonstrating the cost-effectiveness of salbutamol, a synthetic measure, the 'episode-free day', was devised to measure days free of an adverse event or an asthma episode, defined as an asthma attack, the need for rescue medication or sleep disturbance caused by asthma (14).

The analysis adopted in this study is closest to the second approach, reporting effectiveness in meeting the different goals of asthma management separately. In this study, it was not possible to explore the impact of treatment on mortality (there were no deaths recorded in the trials) or on health-related quality of life (data had not been collected in any of the studies). However, it was possible to evaluate the differential impact of the two drugs on the other main goals of asthma management. As such it is one of the first analyses to characterize cost-effectiveness using a comprehensive range of endpoints, enabling decision-makers to compare the economic implications of asthma therapy with fluticasone propionate and budesonide based on a range of endpoints of importance.

Methods

The analysis was conducted from the perspective of the health-care system. All studies comparing budesonide with fluticasone propionate at half, or less than half, of the microgram dose of budesonide, which included daily morning peak expiratory flow rate (PEFR) as an outcome measure in patients with asthma, and which were completed before December 1995, had been included in the clinical meta-analysis and therefore included in this retrospective economic analysis. In each of the seven studies identified (15–21), all patients recorded morning PEFR, severity of daytime and night-time asthma symptoms, use of rescue bronchodilator medication and the incidence of exacerbations each day on a diary card during the run-in and treatment periods. Measurements recorded during the week prior to administration of the first dose of inhaled corticosteroid were used to determine mean pre-study values. The economic evaluation was conducted from a health-care payer's perspective.

MEASURES OF EFFECTIVENESS

Four measures of effectiveness were pre-determined for economic evaluation. For improvements in lung function, two success criteria were defined: an increase in mean morning PEFR of $\geq 15\,l\,min^{-1}$ between pre- and end-of-treatment; and a successfully treated week, defined as a week in which there was an improvement in mean morning PEFR of $\geq 5\%$ from baseline (11). For consistency, the end-of-treatment values used in these lung function-based measures of effectiveness were taken as the mean of the 7 days that ended 3 days before the last days of intended treatment.

For symptom control, the measure was symptom-free day defined as a 24-h period without any asthma symptoms being experienced by the patient, as recorded on the daily diary card. For management of symptoms and exacerbations, the episode-free day was used (14).

COSTS

Total direct health care costs of treatment were calculated by applying published unit costs to health care resource use recorded during the studies. Resource use was identified from data recorded by the patient in the daily diary card (relief medications), and by the investigator in the concurrent medication forms [prescription only treatments for asthma and those associated with asthma exacerbations or side-effects (in effect, treatments for oral candidiasis)] and serious adverse event forms (incidence and duration of hospitalizations). Study medications were costed based on the dose and frequency specified in the study protocols. Standard data collection methods were used across the studies. To account for patient withdrawals and missing data, two major assumptions were made in the assessment of resource utilization.

1. Patients who withdrew, or were withdrawn, from a study were included in the analysis on the assumption that they were treatment failures. A patient withdrawing early from the study was assumed to continue using resources at the same rate as was being used in the time up to withdrawal, but to incur no further treatment benefits.
2. Information on primary care and emergency room visits had not been recorded in any of the studies. It was therefore assumed that a GP visit took place once following an asthma-related hospitalization and once whenever there was a change in asthma-related prescription therapy, or on new prescription of drug treatment for exacerbations or oral candidiasis. Emergency room visits were assumed to have occurred if there was evidence of intravenous treatment of severe acute asthma in the absence of a hospitalization. Hospitalizations had been recorded; where duration of hospitalization was not completed, the U.K. average length of stay for an asthma inpatient episode was used.

The costs of drugs were obtained from the British National Formulary in March 1995, and unit costs for other health-care resources were based on data from the Office of Health Economics (22). Mean overall health care costs (1995 values) were calculated for each treatment arm.

TABLE 1. Studies which provided data for meta-analysis

Study (Ref)	Population	Duration (weeks)	Fluticasone propionate (μg day^{-1})	Budesonide (μg day^{-1})
1. (20)	Adults with severe asthma	12	800 Diskhaler™	1600 Turbuhaler™
2. (21)	Steroid-naïve adults with moderate asthma	6	500 MDI	1200 Turbuhaler™
3. (18)	Adults with moderate asthma	4	500 Diskus™	1200 Turbuhaler™
4. (15)	Adults with moderate asthma	8	400 Diskhaler™	800 Turbuhaler™
5. (19)	Paediatric	4	200 Diskus™	400 Turbuhaler™
6. (16)	Adults with mild/moderate asthma	8	200 MDI	400 MDI
7. (17)	Adults with mild asthma	8	200 Diskhaler™	400 Turbuhaler™

MDI, metered-dose inhaler.

COST-EFFECTIVENESS ANALYSIS

Mean cost-effectiveness ratios (cost per symptom-free day, for example) were calculated and compared across treatment arms for each effectiveness endpoint. Incremental cost-effectiveness ratios (additional cost per additional symptom-free day, for example) were calculated for each effectiveness parameter as the difference in the appropriate average treatment costs between fluticasone propionate and budesonide divided by the difference in success rates. In order to generate these overall cost-effectiveness ratios, the cost-effectiveness ratios for each study were calculated, and then pooled by weighting by the number of patients in the study. The cost per symptom-free day, for example, was calculated by first deriving individual study results (dividing the average treatment cost by the average success rate in each study) and then generating an overall result from the weighted average of the cost-effectiveness ratios in the seven studies.

SENSITIVITY ANALYSIS

A potential criticism of economic evaluations is that arbitrary thresholds or assumptions may be chosen: to address this, sensitivity analyses should be performed to explore the impact of varying the assumptions made. In order to evaluate the robustness of the data to assumptions used in this study, sensitivity analyses were conducted on the results for effectiveness and for cost.

1. The threshold for success was varied for the effectiveness measures based on lung functioning, first with the level of improvement in mean morning peak flow defining a successfully treated week varied between 1 and 10%, and then with the level of improvement in mean morning peak flow defining a successfully treated patient varied between 5 and 30 l min^{-1}.
2. In those patients where the length of stay in hospital was missing, as stated above, the mean U.K. inpatient duration was used. However, as hospitalization was anticipated to be a major cost driver in this analysis, the length of stay for those patients was also varied from 1 to 10 days as part of the sensitivity analysis.

STATISTICAL ANALYSIS

Data from the intention-to-treat populations from all the studies were used in the statistical analyses. Statistical differences between the two treatment arms were tested for all effectiveness measures. The mean proportion of patients experiencing a 15 l min^{-1} improvement in PEFR was compared between treatments using a chi-squared test. The mean proportion of successfully treated weeks, symptom-free days and episode-free days were compared between the treatments using a Student's *t*-test.

Results

The seven studies involved in the meta-analysis on which this economic analysis is based are summarized in Table 1. The original clinical meta-analysis demonstrated that fluticasone propionate significantly improved mean morning PEFR compared with budesonide, with a mean difference in improvement of 11 l min^{-1} (9).

In this economic evaluation, a significantly higher number of patients receiving fluticasone propionate (49%) experienced a minimum improvement in mean morning PEFR of $\geq$15 l min^{-1} compared with 41% of those receiving budesonide ($P<0{\cdot}001$). For the other lung function measure, the mean proportion of successfully treated weeks was 41·7% for fluticasone propionate, compared with 34·1% for budesonide ($P<0{\cdot}001$). Assessing asthma symptom control, the mean percentage of symptom-free days was 41·7% for fluticasone propionate and 38·2% for budesonide ($P=0{\cdot}036$). For control of symptoms and exacerbations and the absence of adverse events, the proportion of episode-free days was 31·0% for fluticasone propionate and 26·7% for budesonide ($P<0{\cdot}003$). In summary, all measures demonstrated significantly greater benefits with fluticasone propionate than budesonide.

The total cost per patient is summarized by treatment arm in Table 2. Overall, mean weekly costs per patient were £12.33 for budesonide and £7.78 for patients treated with fluticasone propionate (daily costs were £1.76 and £1.11, respectively). The main contributing factor to the higher

TABLE 2. Weekly treatment costs*

	Fluticasone propionate (£)	Budesonide (£)
Study drug	5·70	6·22
Rescue medication	0·20	0·22
Treatment of adverse events	1·35	1·40
Health-care contacts	0·57	4·53
Overall	7·78	12·33

*The cost of drugs was based on the U.K. price listed in the British National Formulary in March 1995; unit costs for other health-care resources, e.g. cost of in-patient care, community health-care contacts, were based on data from the Office of Health Economics.
The total values may differ slightly from the sum of the individual items because of rounding the values to the nearest £0·01.

costs of asthma management with budesonide were the higher costs of health care, in particular hospitalization costs. Overall, the cost of health care contacts was £0.57 per week for fluticasone propionate compared to £4.53 per week for budesonide.

Therefore, these results demonstrate that treatment of asthma patients with fluticasone propionate is both cheaper, in terms of overall health care costs, and more effective. Table 3 summarizes the comparative cost-effectiveness of the two corticosteroids for all parameters, i.e. improvement in mean morning PEFR $\geq 15\,l\,min^{-1}$, successfully treated weeks, symptom-free days and episode-free days. For each of these parameters, fluticasone propinate was more cost-effective than budesonide, as demonstrated by the lower cost-effectiveness ratios. In decision making, incremental cost-effectiveness ratios (ICERs) are most useful to interpret as they assess the additional costs required to achieve additional benefits. However, in this study ICERs were not calculated for any of the end-points as in all cases the additional benefits

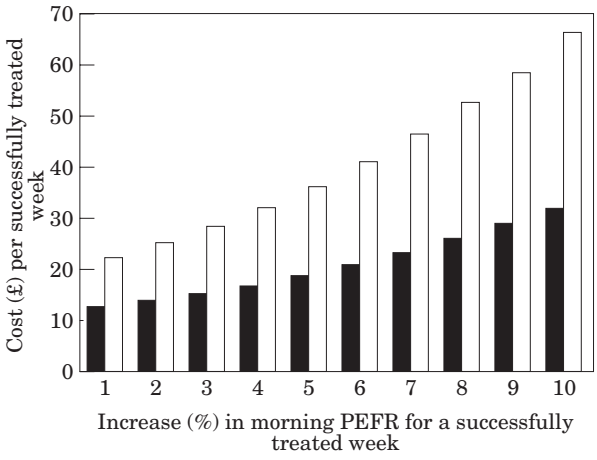

FIG. 1. Sensitivity analysis: cost per successfully treated week (■, fluticasone propionate; □, budesonide).

provided by fluticasone propionate were generated at a lower overall cost, making their calculation redundant.

As part of the sensitivity analysis, the base case for a successfully treated week of 5% mean improvement in PEFR over baseline was varied from 1 to 10% PEFR. This showed that the difference in cost-effectiveness in favour of fluticasone propionate increased as the level of improvement required to define success increased (Fig. 1). A similar result was seen when the criterion for improvement in PEFR over the study period was varied between 5 and $30\,l\,min^{-1}$ (Fig. 2).

When the assumed duration of hospitalization was varied in patients whose length of stay was not recorded, it was shown that the overall costs of care for the two treatments remained in favour of fluticasone propionate. Mean daily costs for fluticasone propionate remained at £1.11 (as there were no missing hospitalization data in these patients), whilst costs in the budesonide arm varied from £1.38 (assuming a length of stay of one day where the duration was missing) to £2.23 assuming the missing lengths of stay to be 10 days). However, across all variations of the sensitivity analysis, treatment with fluticasone propionate remained cheaper overall (and hence more cost-effective) than budesonide.

TABLE 3. Summary of comparative mean cost-effectiveness ratios

	Mean cost-effectiveness	
Cost effectiveness endpoint	Fluticasone propionate (£ patient^{-1})	Budesonide (£ patient^{-1})
Cost per improvement in mean morning PEFR >15 l min^{-1} over study period	2·55	5·51
Cost per successfully treated week	19·45	41·20
Cost per symptom-free day (24 h period)	2·79	4·64
Cost per episode-free day	4·23	7·31

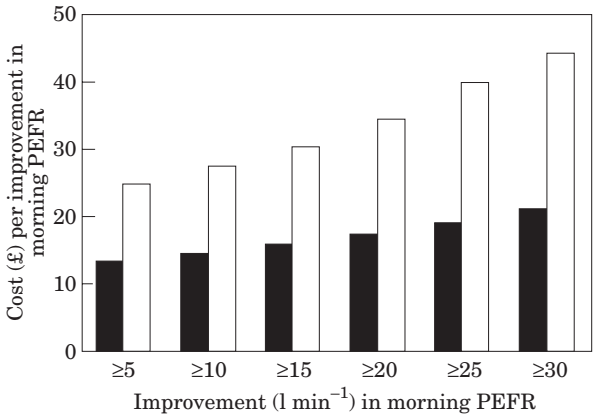

FIG. 2. Sensitivity analysis: cost per improvement in morning peak expiratory flow rate (PEFR) (■, fluticasone propionate; □, budesonide).

Discussion

The cost-effectiveness of treatments is now subject to increasingly detailed scrutiny as the cost of health care increases and government departments attempt to keep down costs in an environment where regulatory agencies are approving drugs at a faster rate than before. The treatment of asthma therefore, like any other disease, is becoming the subject of stringent economic evaluation.

Several studies have assessed the costs and cost-effectiveness of inhaled steroids in the management of asthma prior to this study. In clinical practice, an economic analysis of the addition of inhaled corticosteroids to existing inhaled bronchodilator treatment showed that while drug acquisition costs can be up to three times higher in patients treated with corticosteroids and bronchodilators, these increases are offset by a reduction in other health care costs, such as hospitalization and loss in productivity, resulting in an overall savings in the use of other health care resources (23). Similarly, economic evaluation of asthma therapies in primary care have been reported by Price and Appleby (24) who demonstrated that, although prescribing fluticasone propionate to asthma patients in general practice increased drug acquisition costs, it was accompanied by a reduction in other health care costs which offset the increased prescribing costs.

Asthma is a chronic condition and because the duration of treatment of the studies used in this economic analysis is relatively short (4–12 weeks), assessment of long-term effectiveness and cost-effectiveness was not possible. In the absence of evidence to suggest that the differences in effectiveness would not be sustained, it can be assumed that the longer the treatment period the greater the benefits and the cost savings with fluticasone propionate.

This study represents the first large-population economic evaluation of two frequently prescribed inhaled corticosteroids administered under clinical trial conditions at clinically equivalent doses. Smaller population economic evaluations involving fluticasone propionate and budesonide have already been published. Studies involving budesonide in adults and children with asthma have demonstrated that the increased cost of adding the inhaled corticosteroids to regular or intermittent bronchodilator administration was offset by a reduction in other health-care costs (13,23,25). Moreover, budesonide at dosages of 400–800 μg day^{-1} was significantly better than placebo when evaluated by how much a patient was theoretically willing to pay to avoid asthma and its related complications (26). With respect to comparative fluticasone propionate–budesonide studies, one study (27) demonstrated that in steroid-naïve patients, treatment with fluticasone propionate via a metered-dose inhaler resulted in lower direct health care cost (DM 4·23 *vs.* DM 5·19), lower daily costs per successfully treated patient (DM 9·00 *vs.* DM 12·36) and lowered the cost per symptom-free day (DM 10·58 *vs.* DM 15·26) than budesonide administered at twice the dose via a Turbuhaler™ (Astra Pharmaceuticals). That study formed one of the seven studies on which this meta-analysis was performed. A second study (11) demonstrated that although the fluticasone propionate-treated group was more expensive than the budesonide-treated group, fluticasone propionate was the most cost-effective treatment once the costs were related to outcome levels, and the cost-effectiveness gap widened in favour of fluticasone propionate as the minimum improvement in PEFR used in the definition of success was increased. A third study (28) came to the conclusion that budesonide was more cost-effective than fluticasone propionate. However this evaluation did not use clinically equivalent doses as it used the two drugs at a 1:1 dose ratio whereas, as stated in the British Thoracic Society Guidelines, fluticasone propionate can be considered to be twice as potent as budesonide (4).

Using published economic results for decision-making in a local setting requires not only assessments of the quality and relevance of the evidence, but also estimates of the costs and effectiveness likely to be seen locally rather than in the clinical trial setting, and a judgement over the relative importance or value of the improvements in effectiveness. Although there is debate over the choice of endpoints for measuring effectiveness in economic analyses in asthma, the endpoints used in this study have been used in other published studies and cover most of the goals of asthma management. In interpreting these multiple endpoints for choice of asthma therapy in a local setting, the decision-maker needs to evaluate to what extent the range of improvements in the different outcomes are worth while overall. With the cost savings shown in this study, the results suggest that this will be straightforward: improvements in asthma management can be achieved in parallel with reductions in cost.

Thus, in addition to fluticasone propionate having a greater efficacy:safety ratio than budesonide in both paediatric and adult asthma (9), fluticasone propionate was also most cost-effective than budesonide in these patients.

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